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Homochiral salt of S-Fluoxetine Oxalate: Theoretical Insights on Preferential Crystallization of RS-Fluoxetine Antidepreessant

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Abstract: Fluoxetine (FLX) is a beta-blockers antidepressant drug [1] currently marketed as a racemic salt (RS-FLX). However, due to higher potency of their metabolites, the S-FLX has a higher duration of action than R-FLX [2]. In the present study, S-FLX oxalate was separated by the preferential crystallization of the molecule with oxalic acid on the racemic mixture, and its structure determined by X-ray diffraction. Despite its importance, the chiral recognition mechanism of S-FLX is not sufficiently understood. In order to determine the motives that led to the preferential crystallization of S-FLX, an approximation for the R-FLX oxalate was performed by reversing the configuration of the S-form for the comparative effect of theoretical calculations. All the static calculations were performed using the Density Functional Theory (DFT) with the M062X/6-311G(d, p) level. The estimated lattice energy did not show significant differences for each enantiomer. The rigid potential energy surface (PES) scan of the dihedral angles of FLX (for solution enantiomers) have shown that the S-form has a higher conformational freedom than the approximate R-form. These results suggest that the mechanism leading to the preferential crystallization of the S-FLX probably occurs in crystal formation due to the differences between properties of the enantiomers in solution. With this in mind, another static calculations and Molecular Dynamics (CPMD) simulations was proposed in order to determine the behaviour of the enantiomers in solution with solvent effect.

Key-words: S-fluoxetine, RS-fluoxetine, preferential crystallization, potential energy surface

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